Remarks

Claims 38-89 were pending in the subject application. By this Amendment, claims 38-40, 74, and 76 have been amended, and claims 45 and 88-89 have been cancelled. The undersigned avers that no new matter is introduced by this amendment. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 38-44 and 46-87 are currently before the Examiner for consideration. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a Request for Continued Examination (RCE) under 37 C.F.R. §1.114 for the subject application.

By this Amendment, claims 38-40, 74, and 76 have been amended to recite that the interfering RNA or nucleic acid molecule is administered to hematopoietic cells. Support for this amendment can be found, for example, at page 2, lines 13-17; page 5, line 19; page 7, line 14; page 8, lines 14-17; page 11, lines 3-5 and 31-34; page 13, lines 18-34; and page 17, lines 1-3, of the specification.

Claims 38-89 have been rejected under 35 U.S.C. §112, first paragraph, as lacking sufficient written description and as constituting new matter. The applicant traverses and respectfully submits that the subject specification supports and provides a sufficient written description of the claimed invention. The applicant addresses each of the issues raised in the Office Action in the paragraphs that follow.

The Office Action indicates that the specification does not provide an adequate written description of the inhibitory molecules recited by the claims (interfering RNA specific for SHIP-1 mRNA present in human or mouse hematopoietic cells, and nucleic acid molecules hybridizing *in vitro* under conditions of stringency with human or mouse SHIP-1 mRNA). At page 3, the Office Action indicates that various splice isoforms and sequence variants have been reported for mouse or human SHIP-1. The independent claims recite that the interfering RNA or hybridizing nucleic acid molecule is specific for SHIP-1 mRNA present in human or mouse hematopoietic cells. As explained by Dr. Kerr in the Declaration under 37 C.F.R. §1.132 dated July 16, 2004,

> [a]lthough the potential chimpanzee orthologue is shown on the database to lack a detectable amino-terminal src-homology domain (SH2), it is noteworthy that there is nonetheless 97% nucleotide homology between human SHIP-1 and the chimpanzee sequence. Furthermore, mice and humans are believed to have the same five SHIP-1 protein isoforms. There would be no difficulty in identifying target mRNA sequences shared by all known hematopoietic SHIP-1 isoforms in humans and mice, due to the extensive amount of sequence overlap between the isoforms (see Figure 2A of Rohrschneider *et al.*, *Genes & Development*, 2000, 14:505-520, the full text of which is submitted herewith as Exhibit B). Kerr Declaration, section 4, pages 2-3.

The extent of sequence conservation in the SHIP-1 enzymatic domain, "which one of ordinary skill in the art would likely consider the starting point for selecting any inhibitory hybridizing nucleic acid molecule for SHIP-1, is very high in all five isoforms" (Kerr Declaration, page 3, lines 3-5). Thus, the existence of multiple SHIP isoforms in mouse and human hematopoietic cells does not broaden the scope or complexity of the inhibitory molecules recited in the claims such that the written description requirement is not satisfied.

Based on the high degree of homology between known mammalian SHIP-1 orthologues, and the high degree of conservation between SHIP-1 isoforms, the applicant submits that the subject specification provides an adequate written description of human and mouse SHIP-1 mRNA, as well as mammalian SHIP-1 mRNA. Having the sequence of the target gene (SHIP-1) and knowledge of its structure, including its relevant isoforms, at the time of filing, one skilled in the art could readily envision target nucleic acid sequences within and along the recipient mammal's mRNA. Due to the certainty of the genetic code and nucleotide complementarity, nucleic acid molecules likely to hybridize with SHIP-1 mRNA and interfere with its expression could then be determined. Accordingly, the teaching of the subject specification and knowledge of the sequence and structure of the SHIP-1 gene provides sufficient structural and functional correlates to describe the genus of target mRNA and corresponding interfering RNA and hybridizing nucleotides.

The written description requirement states that the applicant must describe the invention; it does not state that every invention must be described in the same way. The applicant acknowledges that sequences and structural formulas provide a convenient method of demonstrating possession of many molecules; however, other identifying characteristics or combinations of characteristics may demonstrate the requisite possession. In *Enzo Biochem, Inc. v. Gene-Probe, Inc.*, 63 USPQ2d 1609

(Fed Cir. 2002), the Court reaffirmed that deposit of a physical sample may replace words when description is beyond present scientific capability. In *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 65 USPQ2d 1385 (Fed Cir. 2003), the Court explained further that the written description requirement may be satisfied "if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." For example, possession of an antibody may be demonstrated based on a description and characterization of its corresponding antigen. Disclosure of an antigen fully characterized by its structure, formula, chemical name, physical properties, or deposit in a public depository provides an adequate written description of an antibody claimed by its binding affinity to that antigen. *Noelle v. Lederman*, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and MPEP 2163 II.A3(a).

There is no *per se* rule that the need to screen for candidate nucleic acid molecules precludes adequate written description of the nucleic acid molecules. Due to their nature, the interfering RNA and hybridizing nucleic acid molecules recited in the claims are clearly distinguishable from the compounds at issue in Regents of the *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) and *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (Fed. Cir. 2004). In the latter, the Court affirmed that the description of the COX-2 enzyme did not serve to describe unknown small molecules capable of selectively inhibiting the enzyme. The teaching of the subject specification and the knowledge of the sequence and structure of the SHIP gene provides one skilled in the art with sufficient structural and functional correlates to describe the genus of interfering RNA and hybridizing nucleic acid molecules that suppress expression of the SHIP gene in human or mouse hematopoietic cells. The subject specification does not require the screening of vast amounts of candidate small molecule *de novo*, based on function alone, with no guidance provided or available as to the molecular structure of the receptor agonist to be identified. Rather, the teaching of the subject specification, the knowledge of the sequence and structure of the SHIP-1 gene, and the mechanism by which the recited molecules inhibit gene expression, together provide sufficient structural and functional correlates to demonstrate possession of the interfering RNA and hybridizing nucleotides recited in the claims. Identification of specific interfering RNA and specific hybridizing nucleotides would not just be likely, it would be inevitable and imminent. All functional descriptions of genetic material do not necessarily fail to meet the written description requirement as

a matter of law. Rather, the Court has held that the written description requirement may be satisfied if, in the knowledge of the art, the disclosed function is sufficiently correlated to a particular, known structure. *Enzo Biochem, Inc.* Such is the case here. The written description requirement must be considered in the context of the claimed invention and the state of knowledge in the relevant art. *Capon et al. v. Eshhar et al.*, 418 F.3d, 1349 (Fed. Cir. 2005).

At page 4, the Office Action indicates that the subject specification does not mention interfering RNA molecules. However, at page 5, lines 27-34, of the specification expressly teach that the substance that inhibits SHIP function can be a nucleic acid molecule or polynucleotide that binds to, or hybridizes with, SHIP mRNA. In the definition of "nucleic acid" or "polynucleotide" set forth at page 14, lines 7-25, DNA and RNA are clearly contemplated. Furthermore, at page 15, lines 33-34, the specification indicates that DNA can direct production of RNA or a polypeptide that inhibits SHIP. It is well settled that rewording of a passage where the same meaning remains intact is not new matter. *In re Anderson*, 41 F.2d 1237; 176 USPQ 331 (CCPA 1973). The applicant's specification need not describe the claimed invention in *ipsis verbis*. *Ex parte Sorenson*, 3USPQ2d, 1462, 1463 (Bd. Pat. App. & Inter., 1987). The test for determining whether a claimed invention is adequately described in the specification is whether the originally filed disclosure reasonably conveys to a person of ordinary skill in the art that the applicant had possession of the subject matter claimed. *In haec verba* support is not required.

The applicant submits that the subject specification contains sufficient disclosure to convey to one of ordinary skill in the art that the applicant had possession of the claimed subject matter. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 38-66 and 74-89 have been rejected under 35 U.S.C. §112, first paragraph, as non-enabled by the subject specification. The applicant respectfully traverses and submits that the claims are fully enabled by the subject specification.

The sequences of the human and mouse SHIP-1 gene were known at the time the subject application was filed. Furthermore, as indicated above, there is a high degree of homology between known mammalian SHIP-1 orthologues, and a high degree of conservation between SHIP-1 isoforms. Having the sequence of the target gene, SHIP-1, and knowledge of the gene's structure,

one skilled in the art could readily envision target nucleotide sequences within the recipient mammal's mRNA. There would be no difficulty in identifying target mRNA sequences shared by all known hematopoietic SHIP-1 isoforms in humans and mice, due to the extensive amount of sequence overlap between the isoforms. Due to nucleotide complementarity, nucleic acid molecules likely to hybridize with SHIP-1 mRNA and interfere with its expression could then be determined without resort to undue experimentation.

As stated at page 10 of the Office Action, the key issues are whether nucleic acids can be delivered to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity. The applicant has demonstrated that this can be achieved using nothing more than the guidance of the subject specification and what was known by those skilled in the art at the time the patent application was filed.

Figure A of Exhibit G and Exhibit H of Dr. Kerr's previous Declaration dated July 16, 2004, showed that C57BL6/J mice injected i.p. on days 1, 2, and 3 with a SHIP-1 shRNA vector complexed with the cationic lipid DOTAP resulted in significant suppression of all detectable SHIP-1 isoforms in the spleen. Exhibit I and Figure B of Exhibit G showed that pooled siRNA molecules complexed with DOTAP and injected i.v. into C57BL6/J mice resulted in partial suppression of SHIP-1 expression in peripheral mononuclear cells (PBMC) and a significant increase in Mac+Gr1- monocytes and circulating Mac1+GR1+ cells (myeloid suppressor cells), compared to controls. These results show that SHIP-1-specific interfering RNA can have profound physiological effects in a rapid fashion, even when complete knockdown is not achieved. As indicated at page 11, lines 10-34, page 12, and page16, lines 1-18 and 31-34, of the subject specification, various viral and non-viral vectors such as polycationic molecules may be utilized to deliver nucleotides. Column 17 of U.S. Patent No. 6,025,198, which was cited by the Examiner in the previous Office Action, indicates that cationic liposomes may be used to deliver antisense oligonucleotides to inhibit expression of SHIP-2. DOTAP, which was the delivery vehicle utilized by Dr. Kerr in this experiment, has been used for gene delivery to mammalian cells *in vitro* and *in vivo* for some time (see, for example, Porteous D.J. *et al.*, "Evidence for safety and efficacy of DOTAP cationic liposome mediated CFTR gene transfer to the nasal epithelium of patients with cystic fibrosis", *Gene Ther.*, 1997, Mar.,

4(3):210-218; Song Y.K. *et al.*, "Characterization of cationic liposome-mediated gene transfer *in vivo* by intravenous administration", *Hum. Gene Ther.*, 1997, Sept., 8(13):1585-1594).

Referring now to the Declaration under 37 C.F.R. §1.132 dated January 18, 2005, Dr. Kerr indicates that "... even partial induction of SHIP-1 deficiency *in vivo* can increase the representation of cells capable of suppressing allogeneic T cell priming. A reduced allogeneic T cell response is considered by those in the field as a key determinant to successful engraftment" (Kerr Declaration, page 5, section 8). Figures A-C of Exhibit C, which accompanies Dr. Kerr's Declaration, show that induction of SHIP-1 deletion in the adult MXCreSHIPflox/- mice increases MSC numbers in the lymph node (LN) and spleens of mice, and leads to compromised priming of allogeneic T cells. This does not require complete ablation of SHIP-1 expression, as mice with partial SHIP-1 ablation also show significantly reducing priming of allogeneic T cells. As indicated by Dr. Kerr in his Declaration, "the MXCre mouse represents a stringent model for assessment of altered SHIP-1 function, and is recognized by those in the field as a valid tool for determining the physiological effects of endogenous gene ablation *in vivo*" (Kerr Declaration, page 5, section 8). Furthermore, Figures D and E of Exhibit C, which accompanies Dr. Kerr's Declaration, show that SHIPflox/- mice with myeloid-specific expression of Cre (LysCre) have a significant increase in MSC that leads to profound suppression of allogeneic T cell priming. "Again, only a partial deletion of SHIP-1 in the myeloid lineage is required to achieve significant suppression of allogenic T cell responses, which mediate GVHD and organ graft rejection ... [t]hus, this physiologic response is clinically favorable and reasonably correlates with a therapeutic benefit in mediating GVHD and organ graft rejection" (Kerr Declaration, page 5, section 8).

Submitted herewith for the Examiner's consideration is an unpublished Paraiso *et al.* manuscript entitled "Induction of SHIP deficiency prior to allogeneic bone marrow transplant enhances engraftment and survival", of which Dr. Kerr is a co-author. The manuscript demonstrates that induction of SHIP-deficiency in the adult allogeneic bone marrow transplant recipient enhances both the quality and duration of their post-transplant survival. When taken with the other experimental evidence submitted with the applicant's previous responses, it is clear that: (1) SHIP deficiency can be induced just prior to engraftment and still result in enhanced transplant survival; (2) even partial SHIP deficiency will enhance transplant survival; and (3) interfering RNA molecules

can be administered to a mammalian recipient using known delivery methods to achieve the requisite SHIP deficiency.

The applicant respectfully submits that, in view of the disclosure of the subject specification as originally filed, and in view of the experimental results developed using those techniques which are described in the specification and known to those of ordinary skill in the art, compositions and methods for reducing SHIP-1 expression using interfering RNA and hybridizing nucleic acid molecules, as currently recited in the claims, are fully enabled.

Accordingly, the applicant respectfully submits that, given the teaching of the specification and the state of the art in gene suppression using interfering RNA, one of ordinary skill in the art could carry out the claimed methods without the need for undue experimentation. In view of the foregoing remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Claims 67-73 have been rejected under 35 U.S.C. §103(a) as being unpatentable over the combination of Damen *et al.* and Ware, in view of Fire and Gill *et al.* The applicant respectfully traverses and submits that the cited references do not teach or suggest the claimed invention.

As the Examiner is aware, to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP §2142. The Office Action indicates that the motivation for one of ordinary skill in the art to combine the teachings of the cited references is to use RNAi molecules to target and inhibit the expression of SHIP-1 *in vitro* (see page 12, line 22, and page 13, lines 2, 5, and 22 of the Office Action). The Office Action does not set forth a motivation for one skilled in the art to combine the interfering RNA or hybridizing nucleic acid molecule with a pharmaceutically acceptable carrier for the *in vitro* applications recited in the rejection.

Thus, there is no suggestion or motivation in the prior art that would lead a person skilled in the art to arrive at the currently claimed invention. As a matter of law, a finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. Here, it is

only the applicants' disclosure that provides such a teaching, and the applicants' disclosure cannot be used to reconstruct the prior art for a rejection under §103. This was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

> The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 112 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

There mere fact that the purported prior art could have been modified or applied in a manner to yield the applicants' invention would not have made the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Moreover, as expressed by the CAFC, to support a §103 rejection, "[b]oth the suggestion and the expectation of success must be founded in the prior art. . . ." *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531, (Fed. Cir. 1988). In the references cited in support of the §103 rejection, one finds neither.

The applicant respectfully submits that the cited references do not teach or suggest the applicant's claimed invention. In view of the foregoing remarks, reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) is respectfully requested.

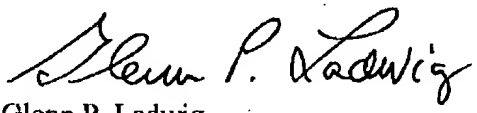
Claims 38-66 and 74-89 have been rejected under the judicially created doctrine of "obviousness-type" double patenting as being unpatentable over claims 12, 13, 22-24, and 33-40 of copending application no. 10/097,101. The applicant respectfully submits that the claims are not obvious over the claims of the cited patent application. However, in order to expedite prosecution of the subject application, the applicant has submitted a Terminal Disclaimer with this Amendment, which obviates this rejection. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

In view of the foregoing remarks and amendments to the claims, the applicant believes that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §§ 1.16 or 1.17 as required by this paper to Deposit Account 19-0065.

The applicant invites the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,



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